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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,026	12/31/2003	Kazuya Mitsuhashi	14879-072002	9499
26161	7590	09/09/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			FRONDA, CHRISTIAN L	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/750,026

Applicant(s)

MITSUHASHI ET AL.

Examiner

Christian L Fronda

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14, 16 and 25 is/are allowed.
- 6) ☒ Claim(s) 15, 17-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/770,517.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/31/03.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 14-25 are pending and are under consideration in this Office Action.
2. Acknowledgment is made of applicants' claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/770,517, filed on 01/26/2001.
3. The paper copy and computer readable form (CRF) of the Sequence Listing file 12/31/2003 have been received and have been processed by the Scientific and Technical Information Center (STIC).
4. The disclosure is objected to because of the following informality: It is noted that this application is a divisional of Application No.09/770,517, filed on 01/26/2001. However, Applicants should update the status of Application No.09/770,517, filed on 01/26/2001, which is now US Patent 6,780,619.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising or consisting essentially of SEQ ID NO: 2 and a substantially purified polypeptide encoded by a nucleic acid comprising SEQ ID NO: 1, does not reasonably provide enablement for any other embodiment as set forth in claims 17-24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the

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state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claims 17-20 encompass any substantially purified polypeptide comprising activity of D-aminoacylase that acts on N-acetyl-D-amino acids to produce the corresponding D-amino acids, wherein the said substantially purified polypeptide comprises any amino acid sequence that is at least 70%, 80%, 90%, and 95% identical to SEQ ID NO: 2, respectively. Since SEQ ID NO: 2 is disclosed as consisting of 558 amino acid residues, then the invention of claim 17 encompasses polypeptides with amino acid sequences that have 391 amino acid residues that are identical to SEQ ID NO: 2 and up to 167 amino acid residues that are different (substitutions, deletions, insertions, and/or additions of with any amino acid residue) from SEQ ID NO: 2 since the claim recites the limitation of 70% identity to SEQ ID NO: 2. Similarly, claim 18 encompasses polypeptides with amino acid sequences that have 446 amino acid residues identical to SEQ ID NO: 2 and up to 112 amino acid residues that differ from SEQ ID NO: 2; claim 19 encompasses polypeptides with amino acid sequences that have 502 identical amino acid residues and 56 amino acid residues that differ from SEQ ID NO: 2; and claim 20 encompasses polypeptides with amino acid sequences that have 530 identical amino acid residues and 28 amino acid residues that differ from SEQ ID NO: 2.

The nature and breadth of claims 21-23 encompass any substantially purified polypeptide comprising activity of D-aminoacylase that acts on N-acetyl-D-amino acids to produce the corresponding D-amnio acids, wherein the said substantially purified polypeptide comprises an amino acid sequence of SEQ ID NO: 2 having any substitutions, deletions, insertions, and/or additions of any of 0 to 50, 0 to 30, and 0 to 10 amino acid residues, respectively. Claim 24 limits the substitutions recited in claim 21 to be conservative substitutions.

In order to meet the enablement requirement, one skilled in the art must be able to make each of the inventions of claims 17-24 without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance on making any of the inventions of claims 17-24 without undue experimentation.

The specification discloses a polypeptide from the fungus *Hypomyces mycophilus* having D-aminoacylase activity and an amino acid sequence of SEQ ID NO: 2 consisting of 558 amino acid residues. However, the specification does not provide guidance or prediction regarding the specific structural and catalytic amino acids residues in SEQ ID NO: 2 that are essential for enzyme activity which cannot be altered. Nor does the specification provide guidance or prediction regarding the specific amino acid residues within the full length polypeptide of SEQ ID NO: 2 that can be changed without destabilizing protein structure and inactivating enzyme activity. Furthermore, the specification does not provide working examples on selecting the specific amino acid residues to change which does not result in loss of D-aminoacylase activity.

The general knowledge of those skilled in the art does not provide any guidance or

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prediction regarding the specific structural and catalytic amino acids residues in SEQ ID NO: 2 which cannot be altered, and specific amino acid residues in SEQ ID NO: 2 that can be changed without destabilizing protein structure and inactivating enzyme activity. The prior art as exemplified by Broun et al. (Science. 1998 Nov 13;282(5392):1315-7) teach that minor modifications to a protein sequence can completely alter the function of a protein. Broun et al. show that as few as four amino acid substitutions in a polypeptide consisting of 380 amino acid residues changes the enzymatic activity of the polypeptide from a desaturase to a hydroxylase (seen entire publication, especially the abstract and pp. 1316-1317).

Since neither the specification nor information known in the art provide guidance or prediction for the specific amino acid residues that can be changed without inactivating enzyme activity, one must perform an enormous amount of trial and error experimentation to determine which 28 amino acid residues in SEQ ID NO: 2 can be changed to make a polypeptide that has an amino acid sequence that is at least 95% identical to SEQ ID NO: 2 and yet has D-aminoacylase activity, in order to meet the limitations of claim 20. Such trial and error experimentation is well outside the realm of routine experimentation and entails selecting any 28 amino acid residues in SEQ ID NO:2 to modify, and searching and screening for the type of modification to perform on the selected 28 amino acid residues (deletion, insertion, substitution, additions or combinations thereof) which will not result in a loss of enzyme activity. Similarly, one must perform an enormous amount of trial and error type experimentation to determine which 167, 112, or 56 amino acid residues in SEQ ID NO: 2 can be changed to make a polypeptide that has an amino acid sequence that is at least 70%, 80%, or 90% identical to SEQ ID NO: 2 and yet has D-aminoacylase activity, in order to meet the limitations of each of claims 17-19, respectively. Teaching regarding screening and searching for the claimed invention using enzyme assays stated in the specification is not guidance for making the claimed invention.

Furthermore, in absence of any guidance or prediction from the specification and information known in the art regarding the specific structural and catalytic amino acids residues in SEQ ID NO: 2 which cannot be altered and specific amino acid residues in SEQ ID NO: 2 that can be changed without destabilizing protein structure and inactivating enzyme activity, one must perform an enormous amount of trial and error experimentation to determine the 0 to 50, 0 to 30, or 0 to 10 amino acid residues in SEQ ID NO: 2 to substitute, delete, insert, or add to SEQ ID NO: 2, in order to meet the limitations of each of claims 21-24, respectively.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid residues which can be changed without inactivating enzyme activity and the specific conservative amino acids that can be substituted for any of the amino acid residues of SEQ ID NO: 2. Without such a guidance, the amount of experimentation left to those skilled in the art to make each of the inventions of claims 17-24 is undue and well outside of routine experimentation. See MPEP § § 2164- 2164.08(c).

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Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Grifantini et al (EP 0677585 A1, published 10/18/1995; PTO 892).

Claim 15 which recites the phrase "consisting essentially of SEQ ID NO: 2", which has not been defined by the specification, is deemed to encompass any polypeptide having an amino acid sequence of SEQ ID NO: 2 containing amino acid residue deletions, insertions, substitutions, additions or combinations thereof.

Grifantini et al. teach a hydantoinase polypeptide having an amino acid sequence that has 123 amino acid residues that are identical to SEQ ID NO: 2 (see attached Alignment SEQ ID NO: 2, Accession AAR82837) and which was expressed in *E. coli* and *B. subtilis*, substantially purified by polyacrylamide gel electrophoresis, and found to have a molecular weight of 50,000 daltons (see Examples 6 and 7 of EP 0677585 A1, pp. 9-10).

The reference hydantoinase polypeptide anticipates claim 15 since the amino acid sequence of the said hydantoinase has an amino acid sequence that has 123 amino acid residues that are identical to SEQ ID NO: 2 and contains amino acid residue deletions, insertions, substitutions, additions or combinations thereof in SEQ ID NO: 2. Thus, the teachings of the reference anticipate the claimed invention.

Conclusion

9. Claims 14, 16, and 25 are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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11. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

 9/3/2004

Christian L. Fronda
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